Am. J. Hum. Genet. 57:603–608, 1995

Spinocerebellar Ataxia Type 1 and Machado-Joseph Disease: Incidence of CAG Expansions among Adult-Onset Ataxia Patients from 311 Families with Dominant, Recessive, or Sporadic Ataxia

L. P. W. Ranum,[1,5] J. K. Lundgren,[1] L. J. Schut,[1] M. J. Ahrens,[2] S. Perlman,[6] J. Aita,[7] T. D. Bird,[8] C. Gomez,[1,5] and H. T. Orr[3,4,5]

Departments of [1]Neurology, [2]Medical Genetics,[3]Laboratory Medicine and Pathology, and [4]Biochemistry and [5]Institute of Human Genetics, University of Minnesota, Minneapolis; [6]Reed Neurological Institute, University of California, Los Angeles; [7]Nebraska Methodist Hospital, Omaha; and [8]Department of Veterans Affairs Medical Center, Seattle.

Summary

The ataxias are a complex group of diseases with both environmental and genetic causes. Among the autosomal dominant forms of ataxia the genes for two, spinocerebellar ataxia type 1 (SCA1) and Machado-Joseph disease (MJD), have been isolated. In both of these disorders the molecular basis of disease is the expansion of an unstable CAG trinucleotide repeat. To assess the frequency of the SCA1 and MJD trinucleotide repeat expansions among individuals diagnosed with ataxia we have collected DNA from individuals representing 311 families with adult-onset ataxia of unknown etiology and screened these samples for trinucleotide repeat expansions within the SCA1 and MJD genes. Within this group there are 149 families with dominantly inherited ataxia. Of these, 3% had SCA1 trinucleotide repeat expansions, whereas 21% were positive for the MJD trinucleotide expansion. Thus, together SCA1 and MJD represent 24% of the autosomal dominant ataxias in our group, and the frequency of MJD is substantially greater than that of SCA1. For the 57 patients with MJD trinucleotide repeat expansions, a strong inverse correlation between CAG repeat size and age at onset was observed ($r = -.838$). Among the MJD patients, the normal and affected ranges of CAG repeat size are 14–40 and 68–82 repeats, respectively. For SCA1 the normal and affected ranges are much closer, containing 19–38 and 40–81 CAG repeats, respectively.

Introduction

The ataxias are a complex group of debilitating and usually fatal neurodegenerative diseases that lead to generalized incoordination particularly affecting gait, speech, and swallowing. These diseases are characterized by progressive degeneration that affects the cerebellum, brain stem, and spinocerebellar tracts, to varying degrees (Greenfield 1954; Harding 1982; Zoghbi 1991). Patients with adult-onset ataxia can be classified into three broad groups that have dominant or recessive inheritance patterns or individuals who have no family history of the disease. A clinical classification system for the ataxias has proved difficult and unreliable because of the clinical variability found both between and within kindreds (Schut 1950; Barbeau et al. 1984; Zoghbi et al. 1988; Orozco Diaz et al. 1990). In recent years, however, much progress has been made toward the development of a genetic classification system for the ataxias. Six different genes that cause dominantly inherited spinocerebellar ataxia have been genetically mapped (Yakura et al. 1974; Jackson et al. 1978; Gispert et al. 1993; Takiyama et al. 1993; Gardner et al. 1994; Ranum et al. 1994, Benomar et al. 1995, Gouw et al. 1995) as have two different genes that cause episodic ataxia (Browne et al. 1994; Kramer et al. 1994). The demonstration that many different genes can cause ataxia may help to explain some of the interfamilial clinical variation noted for the ataxias. The molecular basis for the dramatic variations in age at onset and disease severity that can occur within spinocerebellar ataxia type 1 (SCA1) kindreds was shown to be caused by the expansion of an unstable CAG trinucleotide repeat within a novel gene, ataxin-1 (Orr et al. 1993). Similarly, it was recently demonstrated that the expansion of an unstable CAG repeat in another novel gene is also the mutational mechanism responsible for Machado-Joseph disease (MJD) (Kawaguchi et al. 1994). For both SCA1 and MJD, affected persons with the longest repeat expansions have earlier ages of onset (Orr et al. 1993; Kawaguchi et al. 1994). For SCA1, the most rapidly progressive forms of the disease are found for patients with the longest CAG repeats (Jodice et al. 1994; Ranum et al. 1994).

Received February 17, 1995; accepted for publication June 1, 1995.
Address for correspondence and reprints: Dr. Laura P. W. Ranum, Department of Neurology, Box 295 UMHC, 420 Delaware Street Southeast, Minneapolis, MN 55455.

0002-9297/95/5703-0009$02.00

Although the clinical and genetic heterogeneity of the ataxias present tremendous challenges to understanding this group of diseases, this same diversity also makes the ataxias a critically important group of diseases to study. The eventual isolation and characterization of the different genes that cause ataxia will lead to a better understanding of how various molecular defects lead to differing degrees of neuronal loss in the cerebellum, brain stem, and spinal tracts. To understand more about the ataxias as a group, we have collected DNA samples and clinical data from affected individuals representing 311 families, including 149 kindreds with dominantly inherited ataxia. We have screened these individuals for the SCA1 and MJD gene expansions, to estimate the frequency of these forms of ataxia.

Subjects and Methods

Families Collected

We identified and obtained informed consent and collected blood samples from patients representing 311 ataxia kindreds. Study subjects were recruited by collecting blood samples from affected patients seen by C.G., L.J.S., S.P., J.A., or T.D.B. or through an announcement in the quarterly publication of the National Ataxia Foundation, *Generations*. Study participants were recruited on the basis of a diagnosis of adult-onset ataxia of unknown etiology, without regard to inheritance pattern, disease severity, gender, or ethnic background. No attempts were made to classify or select for patients with specific clinical subtypes of ataxia. Patients with a clinical diagnosis of juvenile-onset ataxia, including Friedreich ataxia, were excluded. None of the 311 kindreds sampled were selected with prior knowledge of linkage information that would indicate a high probability of a certain form of ataxia. To further avoid a disease bias, two kindreds that were previously known to have SCA1, on the basis of linkage analyses, were excluded from the initial frequency analyses. All affected individuals were diagnosed with ataxia by a clinical neurologist and had diagnostic evaluations appropriate to their individual circumstances. Criteria used to exclude patients with ataxia of known etiology included, but were not limited to, evaluation of alcohol consumption, antipurkinje cell antibody screening, thyroid function tests, vitamins B12 and E levels, lysozomal enzymes, phytanic acid levels, very-long-chain fatty acid levels, and magnetic-resonance and computed-tomography imaging. Age at onset was determined on the basis of historical information. For kindreds with a dominant pattern of inheritance, the ethnic background and the ethnic origin of the disease are indicated if the disease could be traced to an ancestor who had emigrated from a specific country (table 1). Although we have no evidence that these families are related, there is a chance that some of the families are represented more than once by different individuals. Blood was collected from at least one affected individual from each of the 311 kindreds represented.

Table 1

Incidence of SCA1 and MJD in Kindreds, by Ethnic Background

	Total	SCA1	MJD
African American	12	0	9
Caucasian American:			
Denmark	1	0	0
British Isles	38	0	2
France	4	1	0
Germany	28	1	11
Italy	5	2	0
Netherlands	4	1	0
Eastern Europe	6	2	0
Portugal	4	0	3
Northwest European	28	0	3
Unknown	16	0	2
Subtotal	134	7	21
Cambodia	1	0	1
Japan	1	0	1
Pakistan	1	0	0
Lebanon	1	0	0
Peru	1	0	0
Unknown	1	0	0
Total[a]	152	7	32

[a] Includes 149 newly identified dominant-ataxia kindreds plus two previously characterized SCA1 families and the MJD-positive patient with no family history of ataxia.

Molecular Studies

Genomic DNA was isolated either from venous blood or from lymphoblastoid cell lines. PCR reactions were performed to screen at least one affected individual from each of these kindreds for the presence of a CAG repeat size within the expanded range for both SCA1 ($\geq$41 repeats) (Ranum et al. 1994; Genis et al. 1995) and MJD ($\geq$68 repeats) (Kawaguchi et al. 1994). For SCA1, primers Rep1 and Rep2 were used (Orr et al. 1993), and for MJD primers MJD25 and MJD52 were used as described by Kawaguchi et al. (1994).

Statistical Analyses

The relationship between age at onset and CAG repeat number on both the affected and normal chromosomes at the MJD locus were evaluated by linear-regression analyses. The frequencies of the SCA1- and MJD-positive patients were initially evaluated by excluding the two kindreds previously known to have SCA1, through linkage studies, and then by including those families for comparison.

Results

Inheritance Patterns

We have collected both clinical information and blood samples from individuals representing 311 different kin-

Table 2

Ataxia Families Represented

	No. (%)
Dominant	149 (48)
Recessive	42 (14)
Sporadic	116 (37)
Unknown	4 (1)
Total	311

dreds. The inheritance patterns for these kindreds are summarized in table 2. Of the 311 families, 149 (48%) were classified as "dominant" because the disease was present in at least two generations and was vertically transmitted from a parent to a child. Kindreds were classified as having a "recessive" ataxia if the disease was present in two or more siblings but there was no evidence of disease in previous generations. Forty-two families (14%) had recessive ataxia. If family history information was available but negative, the patients were classified with sporadic ataxia. There were 116 cases of sporadic ataxia, representing 37% of the total. The inheritance pattern for four of the patients, two of whom were adopted, were classified as unknown because no family history information was available.

Clinical Features

All of the adult-onset patients showed gait and limb ataxia and dysarthria. In addition, the following clinical features were often but not always found: pyramidal tract signs (spasticity, hyperreflexia, and extensor plantar responses); extrapyramidal signs as manifested by movement disorder (e.g., dystonia, parkinsonism); motor weakness and amyotrophy; and ocular motor findings, including one or more of the following—nystagmus, slow saccades, and ophthalmoparesis. In many cases, during the later stages of disease, bulbar findings become evident, leading to swallowing and choking problems. In addition, for some kindreds peripheral neuropathy or retinal degeneration was observed.

Frequency of CAG Expansions for SCA1

Among the 149 dominant kindreds examined for the SCA1 CAG repeat expansion, four families had CAG repeat sizes that were clearly in the affected range (≥41 repeats), and two individuals from families with dominant and recessive forms of ataxia showed repeat sizes in the intermediate range (36–41 repeats), with 40 and 38 repeats, respectively. DNA from these two individuals was sequenced, and additional family members were tested to determine whether these SCA1 alleles were normal or affected.

The patient with 40 repeats was shown to have an uninterrupted repeat configuration consistent with all of the SCA1 kindreds reported elsewhere (Chung et al. 1993). Subsequently, another affected patient from this family was tested for the SCA1 mutation and was shown to have a repeat size within the previously defined affected range (45 repeats), confirming that the original patient was in fact a member of an SCA1 family. A CAG repeat expansion of 40 is the smallest that has been reported for SCA1 to date. These data bring the total number of SCA1 CAG expansions detected among the 149 dominant kindreds to five families, or 3%. When the 2 families that were previously shown to have SCA1 by linkage analyses are included, 7 of 151 families, or 5%, are positive for the SCA1 CAG expansion.

Sequence analysis of the patient with the repeat size of 38 revealed two CAT interruptions. Although this repeat is longer than we typically observe, it is consistent with a normal allele because the CAG repeat is interrupted by CAT trinucleotides (Chung et al. 1993). Blood samples from two additional family members were collected and examined by PCR analysis. An affected brother, as well as an unaffected sister, from this family also had the allele containing 38 repeats. Because the unaffected sister is now 20 years older than the age at which her brothers developed ataxia, and the repeat is interrupted, it likely represents a normal SCA1 allele. While 38 repeats is larger than any of the alleles that we have found in our controls reported elsewhere (Ranum et al. 1994), a normal repeat size of 39 has been reported by another group (Genis et al. 1995). In summary, SCA1 gene expansions were found in 3%–5% of the dominant ataxia kindreds examined and in none of the patients from the families with recessive (n = 42) or sporadic (n = 116) forms of ataxia.

Frequency of CAG Repeat Expansions for MJD

In contrast to the SCA1 results, a much higher number of dominant ataxia families were found to be positive for the MJD trinucleotide repeat expansion. Among the 149 dominant families tested, 31 (21%) had CAG repeat expansions in the affected range (≥68 repeats). No expansions were found among the 42 families with single-generation recessive ataxia (siblings affected), whereas one CAG repeat expansion was observed among the 116 patients classified with sporadic ataxia (table 3). We are currently attempting to obtain blood samples from additional family members, to investigate whether this MJD-positive patient (CAG repeat = 73) truly has a negative family history of the disease and whether there is nonpaternity.

MJD Repeat Size Versus Age at Onset

Fifty-seven affected individuals from the 32 MJD-positive families were examined further, to determine the relationship between the size of the CAG repeat and the

Table 3

Frequencies of SCA1 and MJD

	SCA1	MJD
Dominant	5/149 (3)	31/149 (21)
Recessive	0/42 (0)	0/42 (0)
Sporadic	0/116 (0)	1/116 (1)
Unknown	0/4 (0)	0/4 (0)

NOTE.—Numbers in parentheses are percentages.

age at onset. Three of these families have been reported elsewhere. (Woods and Schaumburg 1972; Aita 1978; Eto et al. 1990; Ranum et al. 1992). Figure 1 shows the correlation of the age at onset and the number of CAG repeats on the MJD chromosomes. The age at onset information was provided by the patient and/or other family members. A linear correlation coefficient (r) of $-.838$ ($P < .0001$) was obtained, indicating that 70% ($r^2 = .703$) of the variation in age at onset can be accounted for by the number of CAG repeat units on the disease chromosome. No significant correlation was found between the size of the CAG repeat on the normal chromosome and the age at onset ($r = .013$; $P = .9241$).

The previously reported range of CAG repeat sizes among normal individuals is 13–36 CAG repeats (Kawaguchi et al. 1994). Among the 56 patients that we examined who were positive for MJD, their normal alleles ranged in size from 14 to 40 CAG repeats, extending the range of normal MJD alleles reported. In addition, the largest expanded allele we detected contained 82 CAG repeats, or was 3 CAG repeats longer than the previously reported range (Kawaguchi et al. 1994).

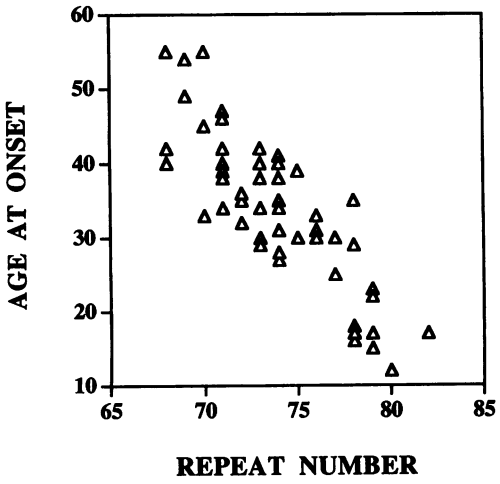

Figure 1 Relationship between the age at onset and the repeat length of the expanded allele, in 57 persons affected with MJD. A linear correlation coefficient (r) of $-.838$ ($P \leq .0001$) was obtained, indicating that 70% ($r^2 = .703$) of the variation in age at onset can be accounted for by the size of the CAG repeat length on the disease chromosome.

Ethnic Background of SCA1 and MJD Families

Table 1 presents the ethnic background and the ethnic origin of disease for the dominant ataxia families. The ethnic origin of disease was indicated when the disease was traced to an ancestor who had emigrated from a specific country. The seven Caucasian American SCA1 kindreds that we have examined trace the disease to ancestors who emigrated from five different European regions. In contrast, for MJD, more than half of the Caucasian families trace the disease to an ancestor who emigrated from Germany. In fact, MJD families that trace their disease origin to Germany represent the largest ethnic group in our study, comprising 11 of 32, or 34%, of the MJD-positive families. African Americans are the second largest MJD-positive ethnic group in our study, with 9 of 12 families positive for MJD.

Discussion

To further the genetic classification of the ataxias, we collected DNA samples from patients representing 311 different ataxia kindreds and screened these patients for the SCA1 and MJD trinucleotide repeat expansions. The frequency of MJD trinucleotide repeat expansions among these samples was substantially higher than for SCA1. Among the kindreds that showed a dominant inheritance pattern, 3% were positive for SCA1, whereas 21% showed MJD gene expansions. No SCA1 or MJD trinucleotide repeat expansions were found among the 42 families with recessive ataxia. In contrast, although no SCA1 repeat expansions were observed among the 116 individuals with sporadic ataxia, one individual with a negative family history of ataxia had an expanded MJD CAG repeat. These results suggest that new mutation events leading to CAG expansions at the SCA1 and MJD loci are relatively rare. Although the frequencies of MJD and SCA1 gene expansions are low among patients who do not have a clearly dominant inheritance pattern, it is important to test these patients, because the implications for families of SCA1- and MJD-positive patients are profound. Two other groups have previously looked for but did not find SCA1 gene expansions among a total of 28 cases of sporadic ataxia (Giunti et al. 1994; Dubourg et al. 1995).

The frequency of SCA1 gene expansions among the dominant kindreds that we examined (3%–5%) is dramatically lower than that reported among a group of Italian and British kindreds (Giunti et al. 1994). Giunti et al. found that 50% (19 of 38) of the dominant ataxia families that they clinically classified with autosomal dominant cerebellar ataxia type 1 had the SCA1 tri-

nucleotide repeat expansion. When all of their autosomal dominant kindreds were included, then 19 of 70, or 27%, showed SCA1 trinucleotide repeat expansions. These differences may reflect differing SCA1 frequencies among the ethnic groups studied and/or potential study biases. For example, if the eight families that were previously mapped to the SCA1 region of 6p had been excluded from the analysis by Giunti et al., then the frequency of SCA1 would be reduced to 18%, or 11 of 62 dominant families.

While the absolute frequencies of SCA1 and MJD will be determined by broad population-based studies that minimize potential biases, we believe that our results accurately reflect a higher frequency of MJD versus SCA1 for the following reasons. First, we collected DNA samples from all volunteers with adult-onset ataxia of unknown etiology, and, thus, there was no intended selection for families based on clinical features, inheritance pattern, disease severity, linkage information, or ethnic background. While volunteer subjects may be more likely to participate in a research study if they are a member of a kindred with a dominantly inherited ataxia and if their ataxia is clinically severe, it is unlikely that there was a significant bias in favor of MJD versus SCA1 patients, because both diseases are dominantly inherited and clinically similar.

We found a highly significant inverse correlation ($r = -.838$) between the size of the MJD repeat and the age at onset, with repeat size accounting for 70% ($r^2 = .70$) of the variation in age at onset. The strong correlation between repeat size and age at onset is similar to that found for SCA1 (Orr et al. 1993; Jodice et al. 1994; Ranum et al. 1994; Genis et al. 1995). For both diseases, however, although there is a strong correlation between these variables, the size of the repeat cannot be used to predict the age at onset accurately (Ranum et al. 1994). For example, among the eight individuals in our group who have an MJD repeat size of 78, the ages at onset range from 16 to 35 years.

The previously reported normal size range for MJD alleles is 13–36 repeats (Kawaguchi et al. 1994). On the basis of the analysis of normal chromosomes from individuals affected by MJD, our data extend the unaffected allele size range to 40 CAG repeats. Thus, the unaffected MJD alleles contain 13–40 CAG repeats, whereas affected alleles for MJD contain 68–82 repeats. For SCA1, the unaffected alleles contain 6–39 CAG repeats, and affected alleles contain 40–81 CAG repeats. The gap between unaffected and affected alleles for MJD is quite large, in comparison with that for SCA1. This difference may reflect the differences in the configurations of the CAG repeat tracts for the two diseases. For example, to date, all of the affected SCA1 alleles reported contain uninterrupted CAG repeat tracts, whereas all but the smallest normal alleles (<21 CAG repeats) are interrupted by one, two, or three CAT trinucleotides. These CAT interruptions are thought to stabilize the repeat tracts on normal SCA1 alleles (Chung et al. 1993). For MJD, although there are interruptions near the 5′ end of the CAG repeat tract, these interruptions are not specific to either the normal or the affected alleles (Kawaguchi et al. 1994). In summary, for SCA1 there are two important changes that occur on affected alleles: one is an increase in the size of the CAG repeat, and a second is the loss of CAT interruptions. For MJD it appears that the size of the CAG repeat is the only factor that distinguishes an unaffected from an affected allele (Kawaguchi et al. 1994), which may account for the larger gap between normal and affected MJD alleles.

It has been postulated that MJD was distributed worldwide in the 16th century by Portuguese navigators and brought by Portuguese immigration to the northeastern and western coastal regions of the United States, locations where others have suggested MJD is commonly found (Rosenberg 1995). Although the frequency of MJD originating from Portugal in the United States is unknown, our observations of a high prevalence of MJD among German emigrants appears inconsistent with the Portuguese as a sole source of MJD in the United States. Now that the MJD gene has been identified, linkage disequilibrium studies can be performed to directly address whether the disease was spread from a single ancestral mutation by Portuguese sailors or arose from multiple mutations throughout the world.

The identification of the SCA1 and MJD genes will provide opportunities to study the molecular bases of these progressive neurologic disorders and should have broad implications for molecular diagnostic testing. The SCA1 and MJD tests combined now make it possible to determine the mutational basis of nearly a quarter of the patients with dominantly inherited ataxia by using simple blood tests. Test availability for SCA1 and MJD should have a significant impact on patient diagnosis and care.

Acknowledgments

We thank the ataxia patients and families for their participation. We thank Donna Gruetzmacher and the National Ataxia Foundation staff for their help in coordinating the participation of study volunteers. In addition, we gratefully acknowledge research support from the Muscular Dystrophy Association, the Bob Allison Ataxia Research Center, the National Ataxia Foundation, and the National Institutes of Health (grant NS33718-01).

References

Aita J (1978) Cranial computerized tomography and Marie's ataxia. Arch Neurol 35:55–56

Barbeau A, Roy M, Cunha L, de Vincente AN, Rosenberg RN, Nyhan WL, MacLeod PL, et al (1984) The natural history of Machado-Joseph disease: an analysis of 138 personally examined cases. Can J Neurol Sci 11:510–525

Benomar A, Krols L, Stevanin G, Cancel G, LeGuern E, David G, Ouhabi H, et al (1995) The gene for autosomal dominant cerebellar ataxia with pigmentary macular dystrophy maps to chromosome 3p12-p21.1. Nat Genet 10:84–88

Browne D, Gancher ST, Nutt JG, Brunt ERP, Smith EA, Kramer P, Litt M (1994) Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, *KCNA1*. Nat Genet 8:136–140

Chung M-y, Ranum LPW, Duvick LA, Servadio A, Zoghbi HY, Orr HT (1993) Evidence for a mechanism predisposing to intergenerational CAG repeat instability in spinocerebellar ataxia type 1. Nat Genet 5:254–258

Doubourg O, Durr A, Cancel G, Stevanin G, Chneiweiss H, Penet C, Agid Y, Brice A (1995) Analysis of the SCA1 CAG repeat in a large number of families with dominant ataxia: clinical and molecular correlations. Ann Neurol 37:176–180

Eto K, Sumi SM, Bird TD, McEvoy-Bush T, Boehnke M, Schellenberg G (1990) Family with dominantly inherited ataxia, amyotrophy, and peripheral sensory loss: spinopontine atrophy or Machado-Joseph Azorean disease in another non-Portuguese family? Arch Neurol 47:968–974

Gardner K, Alderson K, Galster B, Kaplan C, Leppert M, Ptacek L (1994) Autosomal dominant spinocerebellar ataxia: clinical description of a distinct hereditary ataxia and genetic localization to chromosome 16 (SCA4) in a Utah kindred. Neurology 44:A361

Genis D, Matilla T, Volpini V, Rosell J, Davalos A, Ferrer I, Molins A, et al (1995) Clinical, neuropathologic, and genetic studies of a large spinocerebellar ataxia type 1 (SCA1) kindred: (CAG)n expansion and early premonitory signs and symptoms. Neurology 45:24–30

Gispert S, Twells R, Orozco G, Brice A, Weber J, Heredero L, Scheufler K, et al (1993) Chromosomal assignment of the second locus for autosomal dominant cerebellar ataxia (SCA2) to chromosome 12q23-24.1. Nat Genet 4:295–299

Giunti P, Sweeney MG, Spadaro M, Jodice C, Novelletto A, Malaspina P, Frontali M, et al (1994) The trinucleotide repeat expansion on chromosome 6p (SCA1) in autosomal dominant cerebellar ataxias. Brain 117:645–649

Gouw LG, Kaplan CD, Haines JH, Digre KB, Rutledge SL, Matilla A, Leppert M, et al (1995) Retinal degeneration characterizes a spinocerebellar ataxia mapping to chromosome 3p. Nat Genet 10:89–93

Greenfield JG (1954) The spino-cerebellar degenerations. Charles C Thomas, Oxford

Harding AE (1982) The clinical features and classification of the late onset autosomal dominant cerebellar ataxia: a study of 11 families, including descendants of "The Drew Family of Walworth." Brain 105:1–28

Jackson JF, Whittington JE, Currier RD, Terasaki PI, Morton NE, Keats BJB (1978) Genetic linkage and spinocerebellar ataxia. Adv Neurol 21:315–318

Jodice C, Malaspina P, Persichetti F, Novelletto A, Spadaro M, Giunti P, Morocutti C , et al (1994) Effect of trinucleotide repeat length and parental sex on phenotypic variation in spinocerebellar ataxia I. Am J Hum Genet 54:959–965

Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, Katayama S, Kawakami H, et al (1994) CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nat Genet 8:221–228

Kramer PL, Smith E, Carrero-Valenzuela R, Root D, Browne D, Lovrien E, Gancher S, et al (1994) A gene for nystagmus-associated episodic ataxia maps to chromosome 19p. Am J Hum Genet Suppl 55:A191

Orozco Diaz G, Nodarse Fleites A, Cordoves Sagaz R, Auburger G (1990) Autosomal dominant cerebellar ataxia: clinical analysis of 263 patients from a homogeneous population in Holguin, Cuba. Neurology 40:1369–1375

Orr HT, Chung M-y, Banfi S, Kwiatkowski Jr TJ, Servadio A, Beaudet AL, McCall AE, et al (1993) Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nat Genet 4:211–226

Ranum LPW, Chung M-y, Banfi S, Bryer A, Schut LJ, Ramesar R, Duvick LA, et al (1994) Molecular and clinical correlations in spinocerebellar ataxia type I: evidence for familial effects on the age at onset. Am J Hum Genet 55:244–252

Ranum LPW, Rich SS, Nance MA, Duvick LA, Aita JF, Orr HT, Anton-Johnson S, et al (1992) Autosomal dominant spinocerebellar ataxia: locus heterogeneity in a Nebraska kindred. Neurology 43:344–347

Ranum LPW, Schut LJ, Lundgren JK, Orr HT, Livingston DM (1994) A dominant spinocerebellar ataxia gene (SCA5) in a family descendent from the paternal grandparents of President Lincoln maps to chromosome 11. Nat Genet 8:280–284

Rosenberg RN (1995) Autosomal dominant cerebellar phenotypes: the genotype has settled the issue. Neurology 45: 1–5

Schut JW (1950) Hereditary ataxia: clinical study through six generations. Arch Neurol Psychiatry 63(4):535–586

Takiyama Y, Nishizawa M, Tanaka H, Kawashima S, Sakamoto H, Karube Y, Shimazaki H, et al (1993) The gene for Machado-Joseph disease maps to human chromosome 14q. Nat Genet 4:300–304

Woods BT, Schaumburg HH (1972) Nigro-spino-dentatal degeneration with nuclear ophthalmoplegia: a unique and partially treatable clinico-pathological entity. J Neurol Sci 17:149–166

Yakura H, Wakisaka A, Fujimoto S, Itakura K (1974) Hereditary ataxia and HLA genotypes. N Engl J Med 291(3):154–155

Zoghbi HY (1991) The spinocerebellar degenerations. Curr Neurol 11:121–144

Zoghbi HY, Pollack MS, Lyons LA, Ferrell RE, Daiger SP, Beaudet AL (1988) Spinocerebellar ataxia: variable age of onset and linkage to human leukocyte antigen in a large kindred. Ann Neurol 23:580–584